November 21, 2002

Marian Stanley
Manager, Phthalate Esters Panel
The American Chemistry Council
Phthalate Esters Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. Stanley:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Trimellitates Category posted on the ChemRTK HPV Challenge Program Web site on February 20, 2002. I commend The American Chemistry Council Phthalate Esters Panel for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Panel advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Trimellitates Category

SUMMARY OF EPA COMMENTS

The sponsor, the Phthalate Esters Panel HPV Testing Group of the American Chemistry Council, submitted a test plan and IUCLID Data Set to EPA for the Trimellitates Category dated December 13, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 20, 2002. The category consists of four chemicals: 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester; 1,2,4-benzenetricarboxylic acid, triisooctyl ester; 1,2,4-benzenetricarboxylic acid, triisononyl ester; and 1,2,4-benzenetricarboxylic acid, decyl octyl ester.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals under this category is adequate.

2. Physicochemical Properties and Environmental Fate. All appropriate SIDS-level physicochemical properties endpoints have been addressed for the purposes of the HPV Challenge Program. The submitter needs to provide measured biodegradation data for three chemicals. The submitter also needs to provide the input data used for its level III fugacity estimations for TOTM. EPA recommends the level III fugacity model for the remaining three substances.

3. Health Effects. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. However, the submitter needs to address deficiencies in the robust summaries.

4. Ecological Effects. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE TRIMELLITATES CATEGORY CHALLENGE SUBMISSION

Category Definition

The category consists of four substances containing individual trimellitate triesters or mixed trimellitate esters, which are defined as esters of 1,2,4-benzenetricarboxylic acids that have branched or branched and linear alkyl groups ranging in carbon number from C8-C10. The substances included in this category are: 1,2,4-benzenetricarboxylic acid, tris-(2-ethylhexyl) ester (TOTM, CAS No. 3319-31-1), 1,2,4-benzenetricarboxylic acid, triisooctyl ester (TIOTM, CAS No. 27251-75-8), 1,2,4-benzenetricarboxylic acid, triisononyl ester (TINTM, CAS No. 53894-23-8), and 1,2,4-benzenetricarboxylic acid, decyl octyl ester (DOTM, CAS No. 67989-23-5). DOTM is a mixed 1,2,4-benzenecarboxylic acid ester containing 40% decyl and 60% octyl groups. The category definition is clearly stated.

NOTE: TOTM was evaluated in the OECD SIDS Program at SIDS Initial Assessment Meeting (SIAM) 14 held in Paris, France on March 26 - 28, 2002. The Initial Assessment Profile (SIAP) was agreed to at this meeting. The remaining SIDS-related documents are being modified accordingly and will be published in the near future.

Category Justification

The submitter's basis for grouping the members in this category are a common functionality (trimellitate esters) and a narrow range of ester carbon numbers (C8-C10). The submitter states that these structural

features will produce trends in the physicochemical, environmental, and toxicological properties of the four category members. The submitter provided sufficient information and discussion to compare the physicochemical properties of the category members, supporting a conclusion of similar physicochemical properties.

For health and ecotoxicity endpoints, the submitter chose TOTM as an appropriate representative compound to conservatively estimate the properties for the other members because it has the most available data and has the lowest molecular weight of the four materials, and would likely be the most toxic of the category members. The submitter supports this latter conclusion by reference to data from a structurally similar category of chemicals, the phthalate esters, that show greater toxicity in the lower molecular weight members. From the structures of the four substances covered under the category, and by analogy to the phthalate ester category, it is reasonable to expect that TIOTM, TINTM and DOTM will either behave similarly to TOTM, or follow a trend based on the relative molecular weights where TOTM will define the upper toxicity boundary for the toxicological properties of the four esters. Consequently, the information presented by the submitter adequately supports the category for health and ecotoxicity endpoints.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility).

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The data provided by the submitter for photodegradation and stability in water are adequate for the purposes of the HPV Challenge Program.

Biodegradation. EPA disagrees with the submitter's conclusion that no further testing is necessary.

The test plan states that TOTM underwent 4.2% biodegradation in a Japanese MITI test (OECD 301C, *ready* biodegradability) and 68.3 to 71.1% biodegradation after 28 days in another test (the SIAP indicates that TOTM is not readily biodegradable). The test plan and the robust summary disagree as to the description of the MITI test (OECD 301C, *ready* biodegradability, vs. OECD 302C, *inherent* biodegradability). The other TOTM test was described in the test plan as an inherent test, but the robust summary described the result as "readily biodegradable." The submitter needs to address these discrepancies.

Because of the apparent disparity of results in the TOTM studies, the data as presented are not sufficient to describe the biodegradation of the other compounds in this category. The submitter needs to provide measured biodegradability data (following OECD TG 301) for the other three category members.

Fugacity. The submitter uses the Mackay Level I and III fugacity models to determine the partitioning behavior of TOTM. The distributions are provided for releases of 100% to air, 100% to water and 100% to soil. The submitter did not provide the input data for the calculations and needs to supply them. The submitter used Mackay Level I to model the partitioning behavior of the other three trimellitates. Although EPA had previously recommended the use of EQC Level I, this model is somewhat limited. EPA now recommends the use of EQC level III, which is more realistic and useful for estimating a chemical's fate in the environment on a regional basis.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available for TOTM for all health endpoints and for TINTM for the acute oral toxicity endpoint for the purposes of the HPV Challenge Program. The submitter's planned read-across strategy for the data gaps is adequate, and is supported by analogy to data on a structurally similar category, the phthalate esters, and data on the metabolism of TOTM. The submitter needs to address deficiencies in the robust summaries.

Repeated-Dose Toxicity. The submitted data were adequate for TOTM and sufficient to represent other members of the category for the purposes of the HPV Challenge Program.

Reproductive Toxicity. The data submitted for TOTM are adequate and sufficient to represent the other members of the category for the purposes of the HPV Challenge Program.

The submitter needs to correct the statement made in the third paragraph on page 12 of the Test Plan: "In contrast, no reproductive...effects were observed....at dose levels up to 1000 mg/kg/day." The reproductive NOAEL was 100 mg/kg/day for male rats based on the decreases in spermatocyte and spermatid counts at 300 and 1000 mg/kg/day.

Ecological Effects (fish, invertebrates, and algae).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. EPA recommends no testing for this category because the chemicals have log K_{ow} > 8 and low water solubility, and thus no toxicity is expected to occur.

Specific Comments on the Robust Summaries

General Comments.

The submitter needs to provide the purity of the test material for TOTM and TINTM (acute toxicity study) in the IUCLID Data Set Section 1.1 - 1.4. EPA notes that this purity information is included in the Proposed Robust Summary for TOTM.

Environmental Fate.

Fugacity. The submitter uses the Mackay Level I and III fugacity models to determine the partitioning behavior of TOTM. The distributions are provided for releases of 100% to air, 100% to water and 100% to soil. The submitter did not provide the input data used for the calculations and needs to supply them.

Health Effects.

Acute Toxicity. TOTM: Although IUCLID robust summaries for pre-guideline acute oral toxicity studies in male rats and mice provided sufficient information to evaluate the studies, missing information included the strain of animal, the gavage vehicle, and any information on clinical signs or necropsy data (if collected).

TINTM: A IUCLID robust summary for an acute oral toxicty study in male rats provided sufficient information to evaluate the study but omitted the gavage vehicle and any information on body weight effects (if monitored).

Repeated-Dose Toxicity. The IUCLID summary of the same key study on TOTM cited in the SIDS SIAR omitted the group size and organ weight effects. In addition, the IUCLID summary (and test plan) contained incorrect NOAEL/LOAEL values based on an incorrect reading of dose relationships for liver weight effects. The NOAEL was 183 mg/kg/day and the LOAEL was 654 mg/kg/day based on increased relative and absolute liver weights in both sexes at the 0.67 and 2.0% dietary levels, equivalent to 183 and 654 mg/kg/day, respectively.

Genetic Toxicity (in vitro). A IUCLID robust summary for a negative mutation assay in *Salmonella typhimurium* provided sufficient information to evaluate the study but omitted the cytotoxic concentration and the source of the metabolic activation system.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.